

# EXHIBIT E



Comprehensive Cancer Center designated by the National Cancer Institute

2231 6th Street SE  
Room 2-148 CCRB  
Minneapolis, MN 55455  
Phone: (612) 624-7607  
Fax: (612) 624-3869  
hecht002@umn.edu

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Adam M. Slater  
Mazie Slater Katz & Freeman  
103 Eisenhower Parkway  
Roseland, New Jersey 07068

Dear Mr. Slater:

At your request I have reviewed scientific literature, corporate documents, deposition testimony, and regulatory documents and standards, as set forth in this report and the attached Exhibits, and applied my education, training, and knowledge to provide opinions related to the contamination of valsartan manufactured by API manufacturers including ZHP, Hetero, Mylan, and Aurobindo with nitrosamines, and in particular NDMA and NDEA (the "contaminated valsartan"), and then incorporated into finished dose form by the same manufacturers, as well as finished dose manufacturers Teva and Torrent, who purchased the API from the API manufacturers (Teva from ZHP and Mylan, Torrent from ZHP) and incorporated the contaminated valsartan into their finished doses.

As set forth in detail herein, it is my opinion that the NDMA and NDEA levels found in the contaminated valsartan were completely avoidable and therefore are and were unreasonably dangerous, causing an increased risk for the development of cancer for those people ingesting the contaminated valsartan. All opinions set forth herein are held to a reasonable degree of scientific certainty, and have been formed based upon application of scientifically validated methodologies that I utilize in my own scientific work. My background and credentials are set forth in my curriculum vitae, which is attached hereto as Exhibit 1. The list of documents reviewed as part of my analysis is attached hereto as Exhibit 2. The list of scientific literature references specifically relied on for my opinions is attached hereto as Exhibit 3, with the caveat that the scientific literature relevant to the issues addressed is vast, and my familiarity with that literature certainly informs my knowledge in this field, as does all of my experience, even if not specifically listed.

*Stephen S. Hecht*

Stephen S. Hecht, Ph.D.  
Wallin Professor of Cancer Prevention  
American Cancer Society Professor  
American Chemical Society Fellow



considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans.”<sup>46</sup>

ZHP cited to the WHO article in its Deviation Investigation Reports, and Min Li, Ph.D., Vice-President for Analytical Operations for ZHP, confirmed that this was because the article was considered to be scientifically reliable.<sup>47</sup> Dr. Li, who holds a Ph.D. in Organic Chemistry from Johns Hopkins University, also confirmed that ZHP stated in its own Deviation Investigation Report that NDMA is, “a probable, you know, carcinogenic to human.”<sup>48</sup> ZHP also stated in the Deviation Investigation Report for the TEA process that “NDEA is considered as a probably human carcinogen based on projection from the animal studies.” ZHP cited to *Pharmol. Ther.*, 1996, Vol. 71, Nos. 1/2, pp. 57-81 for this. ZHP also cited to *Int. J. Biol. Sci.* 2013, Vol. 9, No. 3, pp.237-245 for the observation that NDEA “is one of the most potent chemical hepatocarcinogens of this class, which can induce a variety of liver lesions in rodents.”<sup>49</sup> Min Li also confirmed that there are no studies deliberately performed on humans with regard to the carcinogenicity of nitrosamines because it would be unethical to knowingly give NDMA to humans, as a result of the risk of cancer. More to the point, Min Li confirmed that it would be unethical “to give humans NDMA in the levels that were found in the valsartan pills.”<sup>50</sup>

Min Li also testified with regard to information provided to ZHP by ZHP’s consulting toxicologist, Charles Wang, Ph.D. Dr. Wang advised ZHP regarding the risk associated with the NDMA and NDEA in the valsartan, and his analysis was the basis for the toxicological assessment found in the Deviation Investigation Reports.<sup>51</sup> Min Li confirmed that Dr. Wang was consulted because he was deemed an expert who would be trusted to provide “reliable information.”<sup>52</sup> Among other things, Dr. Wang advised ZHP that the classification of NDMA as a Class 2A agent was incorrect, and should instead be designated as Class 1B, since, “There are plenty rodent carcinogenicity data for NDMA.”<sup>53</sup> In addition, Dr. Wang consulted what he termed, “a carcinogenicity expert consultant to perform the analysis who knows risk assessment of carcinogen and kept updated in regulatory guideline and standards in this field.” In an email dated July 6, 2018, this expert, James McDonald, Ph.D., advised Dr. Wang – who relayed this information to Min Li - that, “the body of evidence on this suggests pretty clearly that this is a likely human carcinogen at sufficient exposures. The argument that the company would have to make to keep this product on the market will be very difficult with this profile. I’m not exactly sure where one would begin given the very high levels [his understanding was 30 ppm per a prior email from Dr. Wang] you think they are seeing. .... I expect this is not what they would want to hear but, unless there is a compelling reason to leave this product on the market (e.g.: only product available to treat a serious, life-threatening disease), I would expect the FDA would ask for a recall.”<sup>54</sup>

Bandaru Venkata Ramarao, Vice President of Quality Control for Hetero Unit 5 (the finished dose manufacturing division of Hetero) also testified to the

unacceptable increased risk of cancer for those taking the medication. Thereafter, when aberrant peaks demonstrated unaccounted for impurities, the nitrosamine contamination could have been easily discovered based on knowledge of the potential chemical reactions and application of GC-MS to identify potential NDMA/NDEA. This was identified by Novartis even without the full information available to ZHP.<sup>107</sup> These failures and the consequent contamination of the Valsartan API resulted in the dangerous and unreasonable risk of causing or increasing the risk of causing cancer for those who ingested the contaminated valsartan with the reported levels of NDMA and NDEA.

No level of NDMA or NDEA in a pharmaceutical drug is “safe,” in the sense that every exposure increases the risk to some incremental extent that one will develop cancer. The FDA set limits once the valsartan contamination was disclosed, and the aforesaid levels exceed the 96 nanogram/0.3 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDMA, and the 26.5 nanogram/.083 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDEA.<sup>108</sup> Those who ingested the contaminated valsartan above those levels sustained the unreasonably dangerous and unacceptable risk that this would cause or substantially contribute to causing cancer as a result of the NDMA and NDEA contamination.

It is important to note that the FDA’s short term decision to delay the recall of the contaminated valsartan for a very brief period of time was not an endorsement of the safety of the medication.<sup>109</sup> Instead, this was the result of concern over the availability of the medication due to the widespread contamination, and a balancing of the risk of cancer against the more immediate risk of heart attack, stroke, or other life threatening results of a person abruptly ceasing the use of their hypertension medication.

## **2. Nitrosamines in the Hetero API**

Hetero utilized a zinc chloride/DMF/sodium nitrite quenching process that was materially the same as ZHP’s zinc chloride process, and the root cause of the NDMA impurity contamination of Hetero’s valsartan was the same.<sup>110</sup> The reason for this occurring was the same as with ZHP. Mr. Ramarao confirmed this when he agreed with the following: “the most important problem” was that Hetero Unit 1 (API manufacturer) and Unit 5 (finished dose manufacturer) “never even realized the possibility that NDMA could form, so it was never actually looked for. That’s the fundamental problem, correct?”<sup>111</sup>

The NDMA levels found on testing of Hetero’s valsartan API manufactured with the zinc chloride process were confirmed in deposition testimony to range from 0.83 ppm to 7.78 ppm. This data was based on the testing of six batches, and was confirmed to be “representative of the contamination levels across the API – the Valsartan API that was sold from Unit 1 to Unit 5 and then sold in the United States.”<sup>112</sup> As stated, since these impurities resulted from the manufacturing

process, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

### **3. Nitrosamines in the Aurobindo API**

Aurobindo manufactured valsartan API for sale in the United States using a process referred to as the Toluene route, according to deposition testimony from Sanjay Singh, Associate President of North American Technical Operations.<sup>113</sup> The nitrosamine contamination of Aurobindo's valsartan API resulted from cross-contamination caused by a solvent vendor, Lantech.<sup>114</sup> The root causes of this cross-contamination included (1) a contaminated plate in a vertical heat exchanger that was shared between Aurobindo and Mylan, among others,<sup>115</sup> and caused residue to build up and carry over from batch to batch, causing NDEA contamination in the tri-*n*-butyl tin chloride<sup>116</sup> (Aurobindo's Chief Quality Officer analogized this to a dirty microwave),<sup>117</sup> (2) shared tanks (between Aurobindo, Mylan, and others) that were used to store the tri-*n*-butyl tin chloride resulting in NDEA contamination,<sup>118</sup> and (3) Lantech supplied the fresh solvent ethyl acetate which contained TEA,<sup>119</sup> and during the manufacturing process the TEA reacted with nitrosyl chloride, a byproduct of Aurobindo's API manufacturing process, resulting in NDEA contamination.<sup>120</sup>

Both NDMA and NDEA were detected in the valsartan API utilized by Aurobindo. The reported levels of NDEA ranged from 0.028 ppm to 1.508 ppm.<sup>121</sup> The levels of NDMA ranged from below .1 ppm to .129 ppm, and were additive to the NDEA levels, where present.<sup>122</sup> Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

### **4. Nitrosamines in the Mylan API**

Mylan was vertically integrated and supplied valsartan API to Mylan's finished dose manufacturing facilities, and also supplied valsartan API to its sole external United States finished dose customer, Teva.<sup>123</sup> Mylan's root cause investigation found that NDEA was created in the solvent recovery process for o-xylene, the recovery layer of which contained traces of diethylamine and triethylamine, when it was recovered with nitrous acid, and carried over to the final API.<sup>124</sup> Mylan acknowledged that it was warned by its supplier as early as 2014 to

“avoid ... nitrosating agents” with TEA due to the “possibility of formation of nitrosamines with nitrites or other nitrosating agents.”<sup>125</sup>

Mylan confirmed that NDEA was present in every single API batch.<sup>126</sup> Mylan’s API testing confirmed NDEA contamination in every API batch released to the US market, with levels between 0.1 ppm to 1.57 ppm.<sup>127</sup> Dr. Walt Owens, current Head of Global Regulatory Affairs and former Head of Global Quality, testified that “the API and finished dosage form [nitrosamine testing] results were essentially the same, you would be able to test the API alone.”<sup>128</sup> Mylan’s testing also showed that the valsartan API contained sporadic levels of NDMA contamination, in addition to the NDEA, including BQL, BDL, and from 0.01 ppm to 0.09 ppm.<sup>129</sup> Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

## **5. Nitrosamines in the Finished Dose Formulations**

The NDMA and NDEA levels would be expected to be the same or nearly so in the finished dose formulations incorporating the contaminated valsartan API. This was addressed and confirmed in the deposition of Hai Wang, the President of Solco, ZHP’s wholly owned distributor in the United States. Hai Wang confirmed that this was determined by ZHP and that data was provided to the FDA.<sup>130</sup> Both ZHP and Hetero were vertically integrated thus the above discussion of the causes and levels of the nitrosamine contamination of the API addresses the NDMA and NDEA contamination in their finished dose formulations as well.

Finished dose manufacturers Teva and Torrent obtained valsartan API from API manufacturers and then incorporated it into their finished dose formulations.

## **6. Nitrosamines in the Teva Finished Dose Formulation.**

Teva manufactured and sold finished dose valsartan utilizing ZHP manufactured valsartan API, and Mylan manufactured valsartan API, labeled either as Teva or Actavis.<sup>131</sup> The valsartan finished dose labeled as Actavis and sold in the United States initially was manufactured using ZHP TEA process with sodium nitrite quenching valsartan API, and then ZHP zinc chloride process valsartan API beginning in late-2014.<sup>132</sup> The valsartan finished dose labeled as Teva was manufactured using Mylan valsartan API.<sup>133</sup>

ZHP reported NDMA levels to Teva between 0.8 ppm and 240.1 ppm.<sup>134</sup> Teva also tested 83 batches of ZHP valsartan API with NDMA levels of 30.01 ppm to 221.63 ppm.<sup>135</sup> In addition, Teva tested six batches of its finished dose valsartan